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EXAMINER	
SPECTOR, L	
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DATE MAILED: 01/24/96

This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

☒ This application has been examined ☒ Responsive to communication filed on 8/10/95 ☐ This action is made final.

A shortened statutory period for response to this action is set to expire 3 month(s), 0 days from the date of this letter. Failure to respond within the period for response will cause the application to become abandoned. 35 U.S.C. 133

Part I THE FOLLOWING ATTACHMENT(S) ARE PART OF THIS ACTION:

1. ☒ Notice of References Cited by Examiner, PTO-892.
2. ☐ Notice of Draftsman's Patent Drawing Review, PTO-948.
3. ☐ Notice of Art Cited by Applicant, PTO-1449.
4. ☐ Notice of Informal Patent Application, PTO-152.
5. ☐ Information on How to Effect Drawing Changes, PTO-1474.
6. ☐ _____

Part II SUMMARY OF ACTION

1. ☒ Claims 1,3,4,7,9,28,30-40 are pending in the application.
   Of the above, claims _____ are withdrawn from consideration.
2. ☒ Claims 2,5,6,8,10-27,29 have been cancelled.
3. ☐ Claims _____ are allowed.
4. ☒ Claims 1,3,4,7,9,28,30-40 are rejected.
5. ☐ Claims _____ are objected to.
6. ☐ Claims _____ are subject to restriction or election requirement.
7. ☒ This application has been filed with informal drawings under 37 C.F.R. 1.85 which are acceptable for examination purposes.
8. ☐ Formal drawings are required in response to this Office action.
9. ☐ The corrected or substitute drawings have been received on _____. Under 37 C.F.R. 1.84 these drawings are ☐ acceptable; ☐ not acceptable (see explanation or Notice of Draftsman's Patent Drawing Review, PTO-948).
10. ☐ The proposed additional or substitute sheet(s) of drawings, filed on _____. has (have) been ☐ approved by the examiner; ☐ disapproved by the examiner (see explanation).
11. ☐ The proposed drawing correction, filed _____, has been ☐ approved; ☐ disapproved (see explanation).
12. ☐ Acknowledgement is made of the claim for priority under 35 U.S.C. 119. The certified copy has ☐ been received ☐ not been received ☐ been filed in parent application, serial no. _____; filed on _____.
13. ☐ Since this application apppears to be in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under Ex parte Quayle, 1935 C.D. 11; 453 O.G. 213.
14. ☐ Other

EXAMINER'S ACTION

PTOL-326 (Rev. 2/93)

Part III: Detailed Office Action

This Office Action is in response to applicants amendment filed 8/10/95, which is paper number 9. Claims 2, 5, 6, 8, 10-12, 13-27 and 29 have been cancelled. Claims 1, 3, 4, 7, 9, 28, 30, 31 and newly introduced claims 32-40 are under consideration. Applicants attention is directed to the fact that claims 28, 30 and 31 are under consideration, contrary to applicants statement at page 4 of the amendment.

The objections to the specification under 35 U.S.C. § 112, first paragraph, as set forth at page 10, paragraphs 2-3, the paragraph bridging pages 13-14 of the previous office action regarding the term "non-immunogenic", and page 14, line 7 to page 15, line 6 of the previous Office Action are withdrawn in view of applicants amendments.

The rejection of claims 10 and 12 under 35 U.S.C. §112, second paragraph is moot in view of the cancellation of the rejected claims.

The rejection of claims 9 and 10 under 35 U.S.C. §102(b) is withdrawn in view of applicants' amendments.

Formal Matters:

The disclosure remains objected to because the informalities listed as items (1), (2) and (5) of the previous Office Action at page 5. Appropriate correction is **required** for each item. The Examiner notes applicants intent to submit a corrected sequence listing to reconcile items (1) and (2). Applicants have failed to address item (5), regarding the number of α subunits.

37 C.F.R.§1.821(d) reads as follows:

(d) Where the description or claims of a patent application discuss a sequence listing that is set forth in the "Sequence Listing" in accordance with paragraph (c) of this section, reference must be made to the sequence by use of the assigned identifier, in the text of the description or claims, even if the sequence is also embedded in the text of the description or claims of the patent application.

The claims and/or specification are not in full compliance with 37 C.F.R.§1.821(d), and should

be amended to refer to the appropriate sequence identifier(s) (SEQ ID NO:). For example, see claims 1, 9 and 40. Correction is required.

Double Patenting Rejections:

Claim 1 remains provisionally rejected under 35 U.S.C. 101 as claiming the same invention as that of claim 1 of copending application Serial No. 08/08/196689. This is a *provisional* double patenting rejection since the conflicting claims have not in fact been patented.

The non-statutory double patenting rejection, whether of the obvious-type or non-obvious-type, is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent. *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); *In re Van Ornam*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); and *In re Goodman*, 29 USPQ2d 2010 (Fed. Cir. 1993).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321 (b) and (c) may be used to overcome an actual or provisional rejection based on a non-statutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.78 (d).

Effective January 1, 1994, a registered attorney or agent of record may sign a Terminal Disclaimer. A Terminal Disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 3, 4, 7, 9, 28 and 32-40 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-5, 19 and 20 of copending application Serial No. 08/348657, the continuation of 08/176553 for reasons cited in the previous Office Action at page 6.

This is a *provisional* obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claims 1, 3, 4, 7, 9, 28 and 30-40 are directed to an invention not patentably distinct from

claims 1-4, 6, 7, 24, 26 and 27 of commonly assigned application Serial No. 08/185607 for reasons cited in the previous Office Action at page 7.

Commonly assigned application Serial No. 08/185607, discussed above, would form the basis for a rejection of the noted claims under 35 U.S.C. §103 if the commonly assigned case qualifies as prior art under 35 U.S.C. §102 (f) or (g) and the conflicting inventions were not commonly owned at the time the invention in this application was made. In order for the examiner to resolve this issued, the assignee is required under 37 C.F.R. §1.78(c) to either show that the conflicting inventions were commonly owned at the time the invention in this application was made or to name the prior inventor of the conflicting subject matter. **Failure to comply with this requirement will result in a holding of abandonment of the application.** A showing that the inventions were commonly owned at the time the invention in this application was made will preclude a rejection under 35 U.S.C. §103 based upon the commonly assigned case as a reference under 35 U.S.C. §102 (f) or (g).

Comm. owned.

The non-statutory double patenting rejection, whether of the obvious-type or non-obvious-type, is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent. *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); *In re Van Ornam*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); and *In re Goodman*, 29 USPQ2d 2010 (Fed. Cir. 1993).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321 (b) and (c) may be used to overcome an actual or provisional rejection based on a non-statutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.78 (d).

Effective January 1, 1994, a registered attorney or agent of record may sign a Terminal Disclaimer. A Terminal Disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1, 3, 4, 7, 9, 28 and 30-40 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-4, 6, 7, 24, 26 and 27 of commonly assigned application Serial No. 08/185607 for reasons cited in the previous Office Action at page 7.

This is a *provisional* obviousness-type double patenting rejection because the conflicting

claims have not in fact been patented.

Claims 1, 3, 4, 7, 9, 28 and 30-40 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-8, 24, 26 and 27 of copending application Serial No. 08/196689 for reasons cited in the previous Office Action at page 8.

This is a *provisional* obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

It is noted that this application is a member of a large family of applications, including serial numbers 08/185607, 08/196689, 08/223263, 08/249376, 08/348657 (the continuation of 08/176553) 08/374540 and 08/425016, as well as the divisional applications derived from each of the aforementioned cases. There are myriad possible provisional statutory and obviousness type double patenting rejections which might be made between the claims of the instant application and its various copending applications. It is beyond the resources of the PTO to establish each and every possible double-patenting rejection which might be made among the pending claims. 37 C.F.R. § 1.78(b) provides that when two or more applications filed by the same applicant contain conflicting claims, elimination of such claims from all but one application may be required in the absence of good and sufficient reason for their retention during pendency in more than one application. Applicant is required to either cancel the conflicting claims from all but one application or maintain a clear line of demarcation between the applications. See M.P.E.P. § 822.

The Examiner notes applicants statement that the double patenting issues will be dealt with by cancellation of conflicting claims (in the case of statutory double patenting) and filing of appropriate terminal disclaimers (in the case of obviousness double patenting) .

The following is a quotation of 35 U.S.C. § 103 which forms the basis for all obviousness rejections set forth in this Office action:

> A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject

matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Subject matter developed by another person, which qualifies as prior art only under subsection (f) or (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. § 103, the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 C.F.R. § 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of potential 35 U.S.C. § 102(f) or (g) prior art under 35 U.S.C. § 103.

Claims 1, 3, 4, 7, 9, 28 and 30-40 are rejected under 35 U.S.C. § 103 as being unpatentable over copending application Serial No. 08/185607 for reasons cited in the previous Office Action at page 9.

Copending application Serial No. 08/185607 has a common inventor with the instant application. Based upon the earlier effective U.S. filing date of the copending application, it would constitute prior art under 35 U.S.C. §102(e) if patented. This provisional rejection under 35 U.S.C. §103 is based upon a presumption of future patenting of the conflicting application.

This provisional rejection might be overcome either by a showing under 37 C.F.R. § 1.132 that any unclaimed invention disclosed in the copending application was derived from the inventor of this application and is thus not the invention "by another", or by a showing of a date of invention prior to the effective U.S. filing date of the copending application under 37 C.F.R. § 1.131.

Applicants have failed to address the above rejection in their response to the previous Office Action.

Objections and Rejections under 35 U.S.C. §112:

The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The specification is objected to under 35 U.S.C. § 112, first paragraph, as failing to adequately teach how to make and/or use the invention, i.e. failing to provide an enabling disclosure.

The objection that enablement is not commensurate in scope with claims which encompass variant forms of the particularly disclosed ligands, as set forth in the previous Office Action at page 10, line 27 to page 12, line 1 (pertaining to claims 9, 38 and 39, for example) and at page 12, beginning at line 23 to page 14, line 6 is maintained.

The Examiner notes the amendment of claim 9 to recite *stringent*, as opposed to moderate conditions. While this narrows the scope from the previous wording of the claim, it remains of undue scope for reasons of record, see especially page 13 paragraph 1 of the previous Office Action.

Claims 9, 38 and 39 are rejected under 35 U.S.C. § 112, first paragraph, for the reasons set forth in the objection to the specification.

Claims 1, 3, 4, 7, 28 and 30-40 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 as amended is indefinite because it is not clear whether X is the segment 153-332, or alternatively whether X is *selected from the group consisting of* residues 153-332. The analogous objection applies to claim 32. Additionally, claim 33 should also be amended to use proper Markush language.

Claim 2 is further indefinite as introducing an improper product by process limitation,

wherein it is not clear what structural limitation is imposed by the means of production (recombinant vs. synthetic).

Claim 38 is indefinite (or alternatively improperly dependent) because it is not clear how the nature of the encoding nucleic acid, that is whether it is DNA or RNA, affects the structure of the claimed protein.

Claims 39 and 40 are indefinite because it is not clear whether the word "contains" is intended as closed or open language; is the protein limited to the recited sequence (i.e. "consisting of"), or may it comprise additional matter?

Rejections Over Prior Art:

The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

The following is a quotation of 35 U.S.C. § 103 which forms the basis for all obviousness rejections set forth in this Office action:

> A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.
>
> Subject matter developed by another person, which qualifies as prior art only under subsection (f) or (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. § 103, the examiner presumes that the subject matter of the various claims was

commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 C.F.R. § 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of potential 35 U.S.C. § 102(f) or (g) prior art under 35 U.S.C. § 103.

Claims 1, 3, 4, 7, 9, 28, 32-34, 36 and 38-40 are rejected under 35 U.S.C. § 102(b) as anticipated by or, in the alternative, under 35 U.S.C. § 103 as obvious over McDonald, U.S. Patent Number 5,128,449 (McDonald-1) or by McDonald et al., J. Lab. Clin. Med., 1985 (McDonald-2).

McDonald-1 discloses the purification to homogeneity of a protein from human embryonic kidney (HEK) cell culture medium, which protein was shown to stimulate ^{35}S incorporation into platelets of mice in an immunothrombocytethemic mouse assay (col. 1, lines 25-30). It is stated at column 6 that the protein was homogeneous "as judged by both chromatofocusing and autoradiography of SDS-PAGE." The protein had a molecular weight of 15,000 daltons as determined by SDS-PAGE (col. 3, line 56). McDonald-1 is silent with respect to the glycosylation of the isolated protein, although because the preparation was described as being homogeneous, it is likely that the protein was lacking of extensive N-linked glycosylation. McDonald-1 is also silent with respect to the amino acid sequence of the isolated protein. It would appear, on the basis of biological activity, source, and physical characteristics, that the protein of McDonald is the same as claimed in the instant specification.

McDonald-2 discloses purification of TPO from human embryonic kidney (HEK) cell culture medium. At page 173, McDonald-2 discloses fractionation of the purified protein. Especially of note is "cut 7" of Figure 9, which had a molecular weight >15,000 and is stated to "represent a pure TSF with significant bioactivity".

The sequence limitations of the rejected claims are noted. Due to the similarity of McDonald's protein to that claimed, the particular amino acid sequence is presumed, in the absence of evidence to the contrary, to be an inherent characteristic of McDonald's protein. With respect to particular carboxyl termini recited in various claims, in the event that McDonald's

protein may have varied at the carboxyl terminus, it is considered to be an obvious variant of the recited proteins, as there has been no disclosure of any novel property of activity which results from the truncation of the protein at a particular amino acid residue. It is noted that when a claimed product and product(s) disclosed or made obvious by the prior art reasonably appear to be the same, irrespective of the processes by which they are made, the burden of proof is on Applicant to demonstrate a novel or unobvious difference between the claimed product and that of the prior art (*i.e.*, to show that the product of the prior art does not possess the same material structural and functional characteristics as the claimed product). See In re Best, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and Ex parte Gray, 10 USPQ 2d 1922 1923. McDonald's protein is deemed to have been non-immunogenic to humans, as it is from humans that the protein was obtained. With respect to claim 3, which recites product by process type limitations, these limitations to not appear to introduce any physical limitation on the claimed protein such that McDonald's protein would not be expected to meet the limitations of the claims. With respect to claim 7, which recites the limitation that the protein is unglycosylated, it is noted that McDonald is silent with respect to glycosylation. The PTO does not have facilities for examining and comparing applicant's claimed protein with that of the prior art, and thus applicant has the burden of persuasion to make some comparison between materials in order to establish unexpected properties for the claimed proteins. The burden is upon Applicant to prove by comparative evidence that prior art products do not necessarily or inherently possess characteristics of the claimed proteins. Ex parte Gray, 10 USPQ 2d 1922, In re Best, 195 USPQ 430. Further, it is not clear that a change in the glycosylation state of the protein would render the claimed protein patentably distinct from that of McDonald. In the event that McDonald's protein was glycosylated, it would have been obvious and well within the skill of the ordinary artisan to remove the glycosyl groups using old and well known enzymes to effect the removal of such, the removal of glycosylation being a standard analytical method in the art. Finally, with respect to Claim 28, McDonald's protein is deemed to have met the limitations of being a pharmaceutically acceptable carrier, as it was assayed by administration to mice.

Claims 35 and 37 are rejected under 35 U.S.C. § 103 as being unpatentable over McDonald-1 or -2, either reference in view of Shadle et al., U.S. Patent Number 4,847,325. The rejected claims introduce the limitation that the claimed protein has been modified by the covalent attachment of polyethylene glycol, i.e. "pegylated".

Pegylation of proteins for the purpose of increasing circulating half life is well known in the art, as evidenced by Shadle et al. Shadle et al. disclose the site specific attachment of water soluble polymers to colony stimulating factor-1 (CSF-1). They report that such modification increases the circulating half-life and immunogenicity of the altered protein.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the protein as disclosed by either McDonald reference by the method of Shadle et al., attaching polyethylene glycol or other polymers for the purpose of extending serum half-life and/or solubility of the protein. The person of ordinary skill in the art would have been motivated to do so in view of the teachings of the McDonald references of the clinical potential of TPO taken with the art-recognized advantage of increasing serum half-life of therapeutic proteins, as evidenced by Shadle et al.

Claims 30 and 31 are rejected under 35 U.S.C. § 103 as being unpatentable over Mc Donald-1 or -2 in view of Hill et al. (Exp. Hematol. 20:354). The teachings of McDonald are summarized in the above rejection under 35 U.S.C. §102. Neither McDonald-1 or -2 teaches or suggests combining TPO with another cytokine.

Hill et al., in a paper on partial purification of TPO, state that "A variety of growth factors, used either alone or in combination with other factors, have been demonstrated to support the development of megakaryocytes in vitro." (Page 354, first column.) Such factors include IL-3, EPO and Meg-CSF. They go on to teach that EPO is though to support megakaryocyte colony growth by inducing proliferation of early megakaryocyte precursors, and that TPO (Meg-pot) is thought to induce differentiation and maturation of megakaryocytes in vitro.

It would have been obvious to the person of ordinary skill in the art at the time the invention was made to make a composition comprising both TPO (as taught by McDonald-1 or -

2) and IL-3, EPO or Meg-CSF in view of Hill's teaching that the use of growth factors in combination for such purposes was known in the art at the time the invention was made. The ordinary artisan would immediately have grasped that one wanting to effect development of megakaryocytes would find it desirable to combine growth factors which would, together, effect both proliferation and differentiation of the desired cells, and would therefore have been motivated to make such a composition.

Advisory Information:

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Lorraine M. Spector, whose telephone number is (703) 308-1793. Dr. Spector can normally be reached Monday through Friday, 8:00 A.M. to 4:30 P.M.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Ms. Garnette D. Draper, can be reached at (703)308-4232.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist at telephone number (703) 308-0196.

Certain papers related to this application may be submitted to Group 1800 by facsimile transmission. Papers should be faxed to Group 1800 via the PTO Fax Center located in Crystal Mall 1 (CM1). The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 C.F.R. § 1.6(d)). The Art Unit 1812 Fax Center number is (703) 308-0294. NOTE: If Applicant *does* submit a paper by fax, the original signed copy should be retained by applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers in the Office. **Please** advise the Examiner at the telephone number above when a fax is being transmitted.

Lorraine Spector

Lorraine Spector, Ph.D.
Patent Examiner

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